10/012202

C of C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Number: 6,827,946

Date Issued: December 7, 2004

Name of Patentees: Mark Hirsh, Jane Hirsh, and Whe-Yong Lo

Title of Invention: *COMPOSITIONS CONTAINING BOTH SEDATIVE AND NON-SEDATIVE ANTIHISTAMINES*

ATTN: Certificate of Correction Branch
Commissioner for Patents
P.O Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT DUE TO PTO'S AND APPLICANTS' ERRORS

Sir:

Attached in duplicate is form PTO/SB/44 with at least one copy being suitable for printing.

In accordance with MPEP 1485, the exact page, and/or claim, and line number where the errors occurred in the application as filed are identified herein.

1. The requested correction on the face of the patent is not attributable to an error in the application as filed.

2. Claim 8, page 30, line 20

3. Claim 8, page 31, line 1

4. Claim 9, page 31, line 5

5. Page 2, line 24

6. Page 11, line 14

7. Page 11, line 22

CP 103
085337/00006

8. Page 22, line 7

9. Page 22, line 11

Correction Due to PTO's Error

The correction identified in Error 1 is to correct the United States Patent and Trademark Office's failure to correct the inventorship pursuant to the Decision dated September 9, 2004 granting the applicant's petition to correct the inventorship. As indicated in the Decision, Jane Hirsh and Whe-Yong Lo should be listed as inventors.

It is noted that errors 2-4 are typographical errors by the United States Patent and Trademark Office. In error 2 in claim 8, page 30, line 20, "wherein" should be deleted and replaced with "which". In error 3 in claim 8, page 31, line 1, "antiussive" should be deleted and replaced with "antitussive". In error 4 in claim 9, page 31, line 5, "mount" should be deleted and replaced "amount". Correction of these errors does not involve such changes in the patent as would constitute new matter or require reexamination.

Correction Due to Applicant's Error

It is noted that errors 5-9 are due to clerical and typographical errors by the Applicant, as more fully described below. In errors 5 and 6 on page 2, line 24 and page 11, line 14, "descarboethoxyloratadine" should be deleted and replaced with "desloratadine". As noted in the enclosed printout from the Food and Drug Administration, desloratadine is the more commonly used name for "descarboethoxyloratadine" (see reference number five at the end of the enclosed draft executive summary from the Food and Drug Administration at www.fda.gov/ohrms/dockets/ ac/01/briefing/3737b_03_risk.html). In error 7 on page 11, line 22, "Hbr" should be deleted and replaced with "HBr", which is the correct abbreviation for the hydrobromide salt (see the enclosed product description from www.rxmed.com). In errors 8 and

9 on page 22, lines 7 and 11, "Crosscarmellose" should be deleted and replaced with "Croscarmellose" (see the enclosed product description from www.pformulate.com/croscarmellose.htm). These errors occurred in good faith, and correction thereof does not involve such changes in the patent as would constitute new matter or would require reexamination.

Please issue a Certificate of Correction or a corrected patent, if the Commissioner deems that to be more appropriate, and send the document to:

Customer No. 23579
Patrea L. Pabst
Pabst Patent Group LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, GA 30361

U.S. Patent No. 6,827,946
Issued: December 7, 2004
REQUEST FOR CERTIFICATE OF CORRECTION

The Commissioner is hereby authorized to charge $100, the fee for a Certificate of Correction due to Applicant's error as required by 37 CFR 1.20(a), to Deposit Account No. 50-3129. Applicants believe that no additional fee is required. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

Very truly yours,

PABST PATENT GROUP, LLP

Rivka D. Monheit
Reg. No. 48,731

Date: July 6, 2005

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2152
(404) 879-2160 (Facsimile)

DRAFT..... DRAFT..... DRAFT..... DRAFT ..... DRAFT.....

EXECUTIVE SUMMARY

ABBREVIATIONS

AE	Adverse Event
BID	Twice Daily
CDER	Center for Drug Evaluation and Research
NDA	New Drug Application
OTC	Over-The-Counter
OPDRA	Office Of Post-Marketing Drug Assessment
QD	Once Daily
SAE	Serious Adverse Event
WR	Written Request
AERS	Adverse Event Reporting System

RESUMI

This document summarizes an extensive review of worldwide safety information related to loratadine, fexofenadine, and cetirizine that was conducted by the CDER OTC Switch Review Team in response to a Citizen Petition requesting that these drugs be switched to OTC status. The primary objective of this review was to determine whether there are safety concerns associated with loratadine, fexofenadine, or cetirizine that might preclude their appropriate use in the OTC marketplace. This review did not focus on issues related to effectiveness of these agents in the OTC setting, since there is a long history of OTC marketing of antihistamines. A summary of the safety data for each drug derived from the work-group's review is provided.

BACKGROUND

Allergic rhinitis and related conditions are generally considered amenable to self-diagnosis and self-treatment. Antihistamines as a class have a long history of OTC availability and use in these

overdose situation.[17]

Adverse hepatic events have not been reported to be associated with the use of these antihistamines in AERS to any significant extent, and no notable cases were found in the literature for the relevant moieties. Information regarding the metabolic pathways of these antihistamines is scant, although clemastine, chlorpheniramine and diphenhydramine have been described as substrates and inhibitors of the P450 isoenzyme CYP2D6. While it has been suggested that these agents may be capable of producing clinically relevant interactions at therapeutic plasma concentrations, specific interactions have not been identified.[18]

Recently, the potential for cardiac toxicity and CNS effects, particularly the potential to lower seizure threshold, have been studied primarily for diphenhydramine. This moiety has been found to possess $K_{V(r)}$ channel-blocking properties and it is suggested that administration to individuals who are poor metabolizers or concomitantly using other inhibitors of CYP2D6, may predispose to cardiac or seizure events.[19] While cardiac events have been described very rarely in the literature, and are commonly attributed to the anticholinergic activity of first generation agents, seizures have been more commonly described, particularly in cases of overdosage (see above).

Overall, although generally accepted as appropriate OTC drugs, the first generation antihistamines agents possess a number of safety concerns, some of which are serious, in addition to their widely recognized sedative and cognition-impairing properties. It is not surprising that CNS events predominate for these older antihistamines, given that these agents readily cross the blood-brain barrier. Anticholinergic events are also common, another property predicted by their pharmacology. Both of these types of adverse reactions are less common in the newer generation products.

Although the occurrence rates of adverse events attributable to the OTC antihistamines cannot be directly compared to those of loratadine, fexofenadine, or cetirizine due to the many confounders already discussed, these three products may offer certain safety advantages over the currently available first generation antihistamines, primarily with regard to sedation and cognition. This is not to malign to currently available OTC antihistamines, many of which are labeled as OTC sleep aids, but to acknowledge that a choice of appropriately labeled drug products in the OTC marketplace can be expected to aid the consumer to tailor product selection to one most appropriate to the intended use.

REFERENCES:

1. Weiler, JM et al, *Ann Intern Med* 2000; 132:405-407.
2. *USA Today*, April 12, 2000.
3. *Annals of Intern Med* 2000; 132:354-363.
4. Clemastine, the comparator product in several controlled clinical trials with loratadine, is a first generation antihistamine.
5. Descarboethoxyloratadine, also called *desloratadine*, is the major active metabolite of loratadine. An NDA for *desloratadine* has been submitted and is currently under review in HFD-570.
6. Stockwell, M. "Issues Analysis Summary: Benefit-Risk Assessment of the Approved Therapeutic Product Loratadine (Claritin)," submitted report to the Bureau of Licensed Product Assessment, Therapeutic Products Programme, Health Canada, June 22, 2000.
7. Sproule, BA et al *Int. J. Geriat. Psychiatry* 1999, 14, 851-7.
8. Barone DA, Raniolo J *NEJM* 1980;303(2)107.

9. Strauss, A, *J Clin Psychiatry* 1989 50(4):147.
10. Leighton, KM, *Br Med J* 1982, 13(284):789-90.
11. Ackland FM *Lancet* 1984, 1(8387):1180.
12. Frankel et al *J Toxicol Clin Toxicol* 1993; 31(3):493-6.
13. Emadian SM et al *Am J Emerg Med* 1996; 14(6):574-6.
14. Zgurzynski P, Manno M *Pediatr Emerg Care*1999; 15(6):425-8.
15. Soleymanikashi Y, Weiss NS *Annals of Allergy*1970; 28(10)486-90.
16. Aselton P, Jick H *Am J Epidemiol* 1985 122(1):197.
17. Karch SB *Am J Forensic Med Pathol* 1998; 19 (2):143-7.
18. *Drug Metab Dispos* 1998, 26: 536-9.
19. *Trends Pharma* 2000, 21: 52-56.

ROBITUSSIN® ROBITUSSIN® DM ROBITUSSIN® COUGH & COLD ROBITUSSIN® EXTRA STRENGTH ROBITUSSIN® EXTRA STRENGTH DM ROBITUSSIN® EXTRA STRENGTH COUGH & COLD ROBITUSSIN® PEDIATRIC ROBITUSSIN® PEDIATRIC COUGH & COLD

Whitehall-Robins

Guaifenesin

Guaifenesin - Dextromethorphan HBr

Guaifenesin - Dextromethorphan HBr - Pseudoephedrine HCl

Guaifenesin

Guaifenesin - Dextromethorphan HBr

Guaifenesin - Dextromethorphan HBr - Pseudoephedrine HCl

Dextromethorphan HBr

Dextromethorphan HBr - Pseudoephedrine HCl

Expectorant

Expectorant - Antitussive

Expectorant - Antitussive - Decongestant

Expectorant

Expectorant - Antitussive

Expectorant - Antitussive - Decongestant

Antitussive

Antitussive - Decongestant

Action And Clinical Pharmacology: Guaifenesin, as the expectorant, enhances the output of lower respiratory tract fluid. The enhanced flow of less viscid secretions promotes ciliary action, and facilitates the removal of inspissated mucus. As a result, dry, unproductive coughs become more productive and less frequent.

Dextromethorphan is a synthetic, non-narcotic, centrally-acting cough suppressant. The antitussive effectiveness of dextromethorphan has been demonstrated in both animal and human clinical studies, and the incidence of toxic effects has been remarkably low.

Pseudoephedrine produces vasoconstriction resulting in a nasal decongestant effect.

Indications And Clinical Uses: For the management of coughs associated with cold, bronchitis, laryngitis, tracheitis, pharyngitis and influenza.

Contra-Indications: Hypersensitivity to guaifenesin, dextromethorphan or sympathomimetic amines; marked hypertension; patients who are receiving MAO inhibitors should not take Robitussin DM, Cough & Cold, Extra Strength DM, Extra Strength Cough & Cold, Pediatric or Pediatric Cough & Cold.

Patients with diabetes, heart or thyroid disease, high blood pressure, glaucoma or difficulty in urination due to prostate enlargement should not take Robitussin Cough & Cold, Extra Strength Cough & Cold or Pediatric Cough & Cold.

Precautions: Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of the cough is identified, that modification of the cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

If cough worsens, lasts for more than 1 week or is accompanied by high fever, or in patients with hypertension, consult a physician. Do not exceed recommended dosage. Keep safely out of reach of children.

Adverse Reactions: The following may possibly occur: Robitussin, Robitussin Extra-Strength: nausea, gastrointestinal upset, drowsiness.

Robitussin Cough & Cold, Robitussin Extra-Strength Cough & Cold: nausea, vomiting, dry mouth, nervousness, insomnia.

Robitussin DM, Robitussin Extra Strength DM: drowsiness, dizziness, nausea, vomiting, confusion.

Robtiussin Pediatric: drowsiness, dizziness, nausea, vomiting, stomach ache.

Robitussin Pediatric Cough & Cold: drowsiness, dizziness, nausea, vomiting, stomach ache, insomnia, confusion, CNS stimulation, muscular weakness, dry mouth, palpitation, difficulty in micturition.

Dosage And Administration: Robitussin: Take every 6 hours as follows: Adults 12 years and over: 10 to 20 mL. Children 6 to under 12 years: 5 mL. Children 2 to under 6 years: 2.5 mL. Children under 2 years: consult a physician.

Robitussin DM and Cough & Cold: Take every 6 to 8 hours as

follows: Adults 12 years and over: 10 mL. Children 6 to under 12 years: 5 mL. Children 2 to under 6 years: 2.5 mL. Children under 2 years: consult a physician.

Robitussin Extra Strength, Extra Strength DM and Extra Strength Cough & Cold: Take every 6 to 8 hours as follows: Adults 12 years and over: 10 mL. Children 6 to under 12 years: 5 mL.

Robitussin Pediatric and Pediatric Cough & Cold: Take every 6 to 8 hours as follows: Adults 12 years and over: 20 mL. Children 6 to 12 years: 10 mL. Children 2 to under 6 years: 5 mL. Children under 2 years: consult a physician.

Availability And Storage: Robitussin: Each 5 mL of red, cherry-flavored syrup contains: guaifenesin 100 mg. Nonmedicinal ingredients: alcohol, caramel color, citric acid, flavor, glycerin, invert sugar, FD&C Red No. 40, sodium benzoate, sodium chloride and water. Energy: 15.3 kJ (3.7 kcal). Sodium: <1 mmol (2.8 mg). Bottles of 100 and 250 mL.

Robitussin DM: Each 5 mL of red, cherry-flavored syrup contains: guaifenesin 100 mg and dextromethorphan HBr 15 mg. Nonmedicinal ingredients: alcohol, citric acid, flavors, FD&C Red No. 40, FD&C Yellow No. 6, glycerin, invert sugar, sodium benzoate and water. Energy: 12.4 kJ (3.0 kcal). Sodium: <1 mmol (0.8 mg). Bottles of 100 and 250 mL.

Robitussin Cough & Cold: Each 5 mL of pink, cherry-flavored syrup contains: guaifenesin 100 mg, pseudoephedrine HCl 30 mg and dextromethorphan HBr 15 mg. Nonmedicinal ingredients: alcohol, citric acid, flavors, D&C Red No. 33, FD&C Red No. 40, glycerin, invert sugar, sodium benzoate, maltol and water. Energy: 17.6 kJ (4.2 kcal). Sodium: <1 mmol (0.8 mg). Bottles of 100 and 250 mL.

Robitussin Extra Strength: Each 5 mL of red, cherry-flavored syrup contains: guaifenesin 200 mg. Nonmedicinal ingredients: citric acid, corn syrup, FD&C Red No. 40, flavors, glycerin, polyethylene glycol, propylene glycol, sodium benzoate, sodium carboxymethylcellulose, sodium saccharin, sorbitol and water. Energy: 49 kJ (11.7 kcal). Sodium: <1 mmol (4.1 mg). Bottles of 100 and 250 mL.

Robitussin Extra Strength Cough & Cold: Each 5 mL of red, cherry-flavored syrup contains: guaifenesin 200 mg, dextromethorphan HBr 15 mg, pseudoephedrine HCl 30 mg. Nonmedicinal ingredients: citric acid, corn syrup, FD&C Red No. 40, flavors, glycerin, polyethylene glycol, propylene glycol, sodium benzoate, sodium carboxymethylcellulose, sodium saccharin, sorbitol and water. Energy: 49 kJ (11.7 kcal). Sodium: <1 mmol (4.1 mg). Bottles of 100 and 250 mL.

Robitussin Extra Strength DM: Each 5 mL of red, cherry-flavored

syrup contains: guaifenesin 200 mg, dextromethorphan HBr 15 mg. Nonmedicinal ingredients: citric acid, corn syrup, FD&C Red No. 40, flavors, glycerin, maltol, polyethylene glycol, propylene glycol, sodium benzoate, sodium carboxymethylcellulose, sodium saccharin, sorbitol and water. Energy: 49 kJ (11.7 kcal). Sodium: <1 mmol (4.1 mg). Bottles of 100 and 250 mL.

Robitussin Pediatric: Each 5 mL of red, cherry-flavored syrup contains: dextromethorphan HBr 7.5 mg. Nonmedicinal ingredients: citric acid, flavors, FD&C Red No. 40, glycerin, propylene glycol, sodium benzoate, sodium cyclamate, sorbitol and water. Energy: 14.8 kJ (3.5 kcal). Sodium: <1 mmol (9.3 mg). Bottles of 100 mL.

Robitussin Pediatric Cough & Cold: Each 5 mL of red, cherry-flavored syrup contains: dextromethorphan HBr 7.5 mg and pseudoephedrine HCl 15 mg. Nonmedicinal ingredients: citric acid, FD&C Red No. 40, flavors, glycerin, propylene glycol, sodium benzoate, sodium saccharin, sorbitol and water. Energy: 23.6 kJ (5.6 kcal). Sodium: <1 mmol (1.7 mg). Bottles of 100 mL.

Store at room temperature (15 to 30°C).

Pformulate

Home

Pformulate What?

Excipients

Excipient's Express!!

Services

Suppliers

Resources

Advertising

Email

EXCIPIENTS

Croscarmellose Sodium

*1] **Description:*** Cross linked sodium carboxymethylcellulose White, free flowing powder with high absorption capacity.
Contains no sugar or starch.

*2] **Applications:***

Superdisintegrant	High swelling capacity. Recommended concentration: 0.5 – 2.0%. Can be used up to 5.0% Equally effective at low levels in soluble and insoluble tablets, made by any tableting process. *dissolution accelerator*

*3] **Suppliers:***

Blanver	Solutab® , NF
FMC	AcDiSol ®, NF
JRS	Vivasol®
Vijlak Pharma	IP/BP/USP

Need a supplier? Submit in *Excipient's Express*!!!

*4] **References:***
Solutab®, Technical Brochure, Blanver
AcDiSol ®, electronic data, www.avicel.com, FMC

Pformulate/09/29/2000,

PTO/SB/44 (07-03)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,827,946

DATED : December 7, 2004

INVENTOR(S) : Mark Hirsh, Jane Hirsh, and Whe-Yong Lo

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the face of thee patent after "(75) Inventor: Mark Hirsh, Wellesly, MA (US)" insert -- Jane Hirsch, Wellesley, MA (US) and Whe-Yong Lo, Canton, MA (US) --.
Claim 8, column 12, line 8, delete "wherein" and replace it with --which--.
Claim 8, column 12, line 10, delete "antiussive" and replace it with --antitussive--.
Claim 9, column 12, line 15, delete "mount" and replace it with --amount--.
Column 1, line 51, delete "descarboethoxyloratadine" and replace it with --desloratadine--.
Column 5, line 15, delete "descarboethoxy loratadine" and replace it with --desloratadine--.
Column 5, line 23, delete "(Hbr)" and replace it with --(HBr)--.
Column 9, line 24, delete "Crosscarmellose" and replace it with "Croscarmellose--.
Column 9, line 31, delete "crosscarmellose" and replace it with "croscarmellose--.

MAILING ADDRESS OF SENDER:
Patrea L. Pabst, PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, GA 30361

PATENT NO. 6,827,946

No. of additional copies

⇨ Zero

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

DEC 14 2005

PTO/SB/92 (08-03)
Approved for use through 07/31/2006. OMB 0561-0031
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Patent No. 6,827,946
Dated: December 7, 2004
COMPOSITIONS CONTAINING BOTH SEDATIVE AND NON-SEDATIVE ANTIHISTAMINES
CERTIFICATE OF CORRECTION

Certificate of Mailing under 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTN: Certificate of Correction Branch

on July 6, 2005
Date

Signature

Carla Stone

Typed or printed name of person signing Certificate

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

CP 103/085337/00006